REMARKS

Applicants respectfully request reconsideration of the present application in view of the comments that follow.

Status of the Claims

Claims 137-139 are pending in the subject application. No claims have been amended, canceled, or newly added with this submission. Upon entry of this paper, therefore, claims 137-139 will remain pending and under active consideration.

Statement of the Substance of an Interview

Applicants' counsel would thank Examiner Gambel for courtesies extended during an interview on 28 July 2010. As noted in a contemporaneous "Interview Summary Record," discussion during the interview centered on the present inventors' unexpected discovery that the claimed antagonistic anti-CD40 antibodies exhibit a loss of residual agonistic activity. Although a reduction in *effector* function in IgG4 antibodies harboring a S228P and L235E ("PE") mutation had been described, nothing in the prior art, as illustrated by the references of record, presaged a concomitant loss of agonistic activity nascent to the unmodified antibody.

During the interview it also was explained that, in the particular case of antagonistic anti-CD40 antibodies, residual agonistic activity heretofore had thwarted CD40-based immunotherapy. As the application notes, "it is important that anti-CD40 antagonistic antibodies have no activity to induce signals." Page 27, lines 27 and 28. By virtue of agonistic activity, that is, "however weak it may be, the symptoms [being treated] may worsen in contrast to the desired therapeutic effect." Page 28, lines 3-6. Thus, an "antibody without any agonistic activity is more preferable as a pharmaceutical agent." *Id.*

Examiner Gambel was not heard to dispute the results presented or to question their "unexpectedness". Nevertheless, he cautioned that a new search and study of the prior art would be required, in particular to uncover any suggestion that a loss in agonistic activity would follow from perturbation in F_c receptor crosslinking.

On this latter note, applicants presented evidence to the effect that, even were there a suggestion in the art of some nexus between F_c receptor crosslinking and loss of agonistic activity, the present invention still would be unobvious, within the meaning of Section 103. First, the claimed antibody shows not merely a reduction in agonistic activity but rather no agonistic activity even *in vivo*. Second, the claimed antibody exhibits no agonistic activity *in vivo* even at a concentration more than 50x higher than had been observed in the art, discussed below. Thirdly, the art of record teaches that a PE mutation in IgG4 antibodies can contribute merely to a *reduction* of effector function and not an *abolition* of agonistic activity, as the claimed invention achieves.

The examiner kindly agreed to take these factors into consideration in his reconsideration of this application.

Rejection Under 35 U.S.C. § 103(a)

Claims 137-139 stand rejected over WO 02/088186 to Mikayama *et al.* ("Mikayama PCT") or U.S. Patent No. 7,193,064 to Mikayama *et al.* ("Mikayama") in view of U.S. Patent No. 6,998,124 to Erickson-Miller *et al.* ("Erickson-Miller"), U.S. Patent No. 6,936,698 to Taylor ("Taylor"), and U.S. Patent No. 6,376,653 to Holmes *et al.* ("Holmes"). Office Action at 5-7. Applicants respectfully traverse the rejection.

As highlighted during the July 28th interview, nothing in the cited art even hints at the possibility that a mutation acknowledged to reduce effector function also could abolish residual agonistic activity,[1] heretofore seen as common to antagonistic anti-CD40 antibodies. Indeed, although the "secondary" references discuss at length a loss of *effector* function on account of PE mutations, none teaches or suggests how such mutations of the heavy chain constant region might effect agonistic activity[2] by virtue of the described crosslinking of the antibody to an F_c receptor. *See* Erickson-Miller at col. 11, ll. 48-52, Taylor at col. 6, ll. 60-66, and Holmes at col. 10, ll. 66 – col. 11, ll. 5.

[1] See Example 15 and Figure 16, which show that upon administration of 4D11G4PE antibody to cynomolgus monkeys, no increase in IL-12 production is observed. IL-12 is an indicator of CD40 agonistic activity *in vivo*.

[2] According to the application, "agonistic" activity refers to an action of enhancing binding of a ligand to CD40 expressed on the surface of such cells as B cells, tumor cells or dendritic cells, or an action of providing the

Rather, Reddy *et al.* of record shows that unlike the present invention, the antagonistic anti-CD4 antibody, clenoliximab, *does* exhibit agonistic activity *in vivo*.[3] Reddy's teachings comport with Newman *et al., Clinical Immunology*, 98: 164-74 (2001) (copy attached), which similarly reports that clenoliximab exhibits agonistic activity when administered to chimpanzees at a concentration of just 1.5 mg/kg. Thus, Newman's Figure 5e evidences "a modulation of cell surface CD4 molecules" by clenoliximab (page 171, 2nd column).

Example 15 of the present application shows that the claimed 4D11G4PE antibody does not exhibit *any* agonistic activity *in vivo*. These experiments now have been confirmed, with an additional indicator of CD40 agonist activity (IFNγ[4]) and with a higher dose of 4D11G4PE antibody, in an effort to allay any concern on Examiner Gamble's part that the above-discussed, unexpected benefits pertain only at relatively low doses of the antibody alone. Indeed, 4D11G4PE antibody was administered at a concentration of 100 mg/kg in the present experiment, compared to a dose of 30 mg/kg in Example 15.

The detailed methods and results of the experiment are attached. Briefly, PBS alone (#1 and #2), or with 100 mg/kg of 4D11G4PE (#3-#5), was administered intravenously once weekly for four weeks to male cynomolgus monkeys. Blood was drawn from the femoral vein of the monkeys at indicated time points and assessed for IL-12 or IFNγ by ELISA. The results are summarized as follows:

CD40-expressing cells with at least one effect which the CD40 ligand makes on the CD40-expressing cells. Page 39, lines 11-15.

[3] Details of the disclosures of Reddy have been already explained in previous of applicants' submissions filings and are therefore not reiterated here for compactness of the record

[4] In Example 15, only IL-12 was assessed as an indicator of agonistic activity. IFNγ also is an indicator of agonistic activity, however. *See* Schönbeck, *et al., Int'l J. Biochem. & Cell Biol.* 32: 687-93 (2000) (appended), which implicates the interaction of CD154 (CD40 ligand) with its receptor (CD40) in the modulation of inflammatory responses, such as the induction of adhesion molecule expression of pro-inflammatory cytokines, including IFNγ. See Figure lB and related discussion. Thus, Schönbeck identifies IFNγ as an indicator of CD40 agonistic activity.

Table 1. Serum IL-12 concentrations upon administration of 4D11G4PE[5]

Test no.	0 h	24 h after 1st administration	24 h after 4th administration	7 d after 4th administration
#1	BLOQ	BLOQ	BLOQ	43.1
#2	41.9	13.7	19.4	29.0
#3	BLOQ	BLOQ	15.7	10.4
#4	128.7	82.3	23.6	93.6
#5	58.1	25.3	BLOQ	BLOQ
BLOQ (below the limit of quantification)				

Table 2. Serum IFNγ concentrations upon administration of 4D11G4PE.[5]

Test no.	0 h	24 h after 1st administration	24 h after 4th administration	7 d after 4th administration
#1	47.7	BLOQ	BLOQ	27.1
#2	BLOQ	BLOQ	BLOQ	42.1
#3	BLOQ	BLOQ	BLOQ	BLOQ
#4	4.3	72.7	18.2	34.3
#5	85.4	102.7	64.3	69.3
BLOQ (below the limit of quantification)				

Importantly, these data show that the claimed antibody shows not merely a reduction in agonistic activity but rather no agonistic activity, at a concentration of 100 mg/kg. As applicants' most recent response explained, an antagonistic anti-CD40 antibody holds great promise for therapeutic regulation of cellular immunity and humoral immunity. Despite intense investigation, however, anti-CD40 therapy has not been realized, in part, on the inability to discover such an antagonistic antibody that does not also exhibit some agonistic activity *in vivo*. Indeed, even weak agonistic activity can thwart clinical application of an antibody targeting CD40. See specification at page 28, second full sentence.

[5] Should it concern the examiner, the nominal variations or apparent "increases" in value are, in fact, biologically insignificant.

Taken together, applicants respectfully submit that the claimed antibody manifests properties, which could not have been reasonably predicted by the ordinary artisan at the time of invention. Withdrawal of the subject rejection is thus respectfully solicited.

Obviousness-Type Double Patenting Rejection

Pursuant to the Office Action at page 8, claims 137-139 stand provisionally rejected over claims 1-7 of U.S. application serial No. 11/663,340. Applicants traverse this rejection.

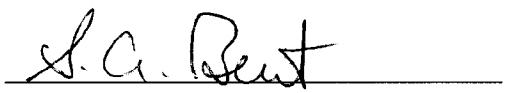
Without acquiescing to the examiner's reasoning or conclusion, the examiner is requested to hold this provisional rejection in abeyance until such time as the claims at issue are deemed otherwise allowable. If any double patenting concern remains at that time, applicants will address the rejection on the merits.

CONCLUSION

Applicants submit that this application is in condition for allowance, and they request an early indication to this effect. Examiner Gambel also is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

Respectfully submitted,

Date August 12, 2010

By 

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Registration No. 29,768
Sunit Talapatra, Ph.D.
Registration No. 54,482

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of the relevant fee(s) from the deposit account.